## Xylazine, Methamphetamines, Bath Salts, and Spice with Dr. Cummings

*Catalina Baas, Michael Cummings, M.D., David Puder, MD*

I am thrilled to continue our podcast series on addiction, designed to meet the one-time, 8-hour training requirement introduced by the Consolidated Appropriations Act of 2023. This mandate applies to all practitioners registered with the Drug Enforcement Administration (DEA), and our series primarily focuses on the treatment and management of patients with substance use disorders.

Here are other episodes that contribute towards the training requirement:

- Episode 182: Opioid Use Disorder with Dr. Cummings (1 CME unit)
- Episode 181: Alcohol Use Disorder with Dr. Cummings (1 CME unit)
- Episode 044: Marijuana and Mental Health (0.5 CME units)
- Episode 064: Does Cannabis Use Increase Schizophrenia and Psychosis? (0.75 CME units)
- Episode 066: Fentanyl: The Next Phase in the Opiate Epidemic (0.75 CME units)
- Episode 030: Ketamine and Psychedelics with Dr. Michael Cummings (0.75 CME units)

All these episodes, along with future releases, are included in our yearly subscription. For registration or additional information about this course, please visit: https://www.psychiatrypodcast.com/cme-program.

We appreciate your dedication to enhancing patient care and tackling the substantial challenges associated with addiction and detoxification. We are eager for your participation in our upcoming CME course, curated with the specific needs of mental health professionals in mind.

We always welcome your suggestions. If there are any addiction experts you'd recommend for me to interview, please do not hesitate to share their names.

Thank you for your unwavering support. Stay tuned for more updates!

# Xylazine

Xylazine (also known as “tranq” or the “zombie drug”) is a clonidine analogue and alpha-2 adrenergic agonist with effects in both the central and peripheral nervous system. It functions as a powerful sedative, analgesic, and muscle relaxant, and has long been used in veterinary medicine as a tranquilizer for animals such as dogs and horses. Xylazine is not FDA approved for use in humans due to potentially dangerous side effects including severe central nervous system (CNS) depression or sedation (U.S. Food and Drug Administration, 2022). Alarmingly,

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xylazine is increasingly being added to drugs sold on the street despite the significant risk it poses.

# Side Effects and Overdose

Xylazine is preferentially mixed with opioids since it acts to prolong and enhance their effects or, put another way, “give [fentanyl] legs.” However, this combination is extremely hazardous, as it increases the risk of fatal overdose. Xylazine induces sedation by reducing  the activity of noradrenergic neurons in the locus coeruleus, which is part of the reticular activating system necessary for maintaining consciousness (Giovannitti et al., 2015). This results in decreased activation of ascending noradrenergic pathways, producing reduced cortical activity and profound sedation for which it is sometimes called the “zombie drug.” When xylazine is combined with opioids, which reduce the brain’s sensitivity to rising CO2 levels, the risk of fatal respiratory depression is magnified. Adding to this risk is the fact that both fentanyl and xylazine can be lethal at very small doses. Importantly, as xylazine is not an opioid, naloxone (Narcan) does not reverse its effects. Even so, providers are still advised to administer naloxone to treat the effects of any opioids taken along with the xylazine.

In addition to sedation and CNS depression, xylazine can produce significant tissue damage and necrosis at IV injection sites. This is believed to be due to vasoconstriction leading to impaired wound healing. The wounds can be so severe as to necessitate amputation (Malayala et al., 2022).

# Xylazine Misuse is Rising

According to the DEA, "xylazine is making the deadliest drug threat our country has ever faced, fentanyl, even deadlier." Mixtures of xylazine and fentanyl have so far been seized in 48 states and, in 2022, “approximately 23% of fentanyl powder and 7% of fentanyl pills seized by the DEA contained xylazine” (Center for Disease Control and Prevention, 2023).

A current challenge with treating xylazine misuse is that the drug is not detected in routine toxicology screens. Thus, the diagnosis involves clinical suspicion. The presence of sedation, severe skin wounds, and poor response to naloxone in a patient with known substance use can be important clues.

# Treatment of Intoxication and Withdrawal

Treatment of opioid/xylazine overdose involves administration of naloxone, securing the airway, providing supplemental oxygen, and treating hypotension (Gupta et al., 2023). There is currently no FDA-approved medication for reversing xylazine. Next, the withdrawal effects must be

addressed. Xylazine withdrawal primarily involves autonomic instability, which can be very severe and may require admission to the ICU. Possible serious complications include stroke, seizures, and myocardial infarction due to rebound vasoconstriction. Options for pharmacologic management are still under investigation. One case study reported success using dexmedetomidine, phenobarbital, tizanidine, and later clonidine (Ehrman-Dupre et al., 2022).

# Methamphetamine

## Overview

Methamphetamine has historically been used medically for weight loss and treatment of ADHD. However, it has since fallen out of favor due to its neurotoxicity and high addictive potential, as well as the advent of alternative medications.

In contrast to the amphetamine salts now used for ADHD management, methamphetamine more rapidly crosses the blood brain barrier, is more potent, and has longer lasting effects (Goodwin et al., 2009). While a typical dose of amphetamine salts is 5-40mg per day, methamphetamine abusers average 100-1000 mg daily (Moszczynska, 2016).

## Mechanism and Side Effects

Methamphetamine is a highly addictive stimulant that exerts its effects by increasing the synaptic release of dopamine, serotonin, and norepinephrine. The mechanism appears to involve displacement of neurotransmitters from transport vesicles, reversal of flow through plasma membrane transporters, and reuptake inhibition (Lin et al., 2016; Kish, 2008).

The flooding of dopamine in the nucleus accumbens, mesolimbic circuitry, and amygdala is also responsible for many of the effects of methamphetamine intoxication, including euphoria, hyperarousal, hypersexuality, agitation, psychosis, and impulsive behaviors such as theft and gambling. Approximately 40% of users experience psychosis, which can involve violent behaviors, paranoid delusions, and hallucinations which commonly involve a feeling of bugs crawling under the skin. These effects are usually transient but may persist in some individuals, making it difficult to distinguish from a primary psychiatric diagnosis (Glasner-Edwards and Mooney, 2014).

As methamphetamine wears off, users can experience a “crash” where they become somnolent and irritable due to depletion of intracellular dopamine stores. Other common symptoms include anhedonia and hyperphagia. In order to stave off the crash and maintain euphoria, users may

go on what's called a "meth run" where they use the drug for several days, often forgoing eating and sleeping (Methamphetamine Research Report, 2016).

Other significant side effects of methamphetamine abuse include tooth decay due to impaired blood supply ("meth mouth"), pupillary dilation, hypertension, stroke, myocardial infarction, arrhythmias, muscle wasting, malnutrition, seizures, and damage to the brain, heart, liver, kidney, and lungs (Yasaei and Saadabadi, 2023). Infections related to IV use are also common.

## Treatment

An acutely intoxicated individual with psychosis can be treated with a low-dose antipsychotic. It is important not to give too high of a dose initially, as the intracellular dopamine depletion present after methamphetamine use can increase the risk of drug-induced parkinsonism and dystonia. Medications such as hydroxyzine can be helpful for acute treatment of anxiety.

After the initial psychosis or agitation is addressed, the patient can be offered supportive care including sleep, food, and fluids. Afterward, patients motivated to quit could benefit from attendance of a treatment program to help maintain abstinence. Therapy can also be highly beneficial, especially for individuals with other underlying psychiatric conditions.

# Effects of Perinatal Drug Exposures

Substance abuse during pregnancy can have lasting effects on the growing child. Potential consequences of commonly abused substances are as follows:

**Methamphetamines**: Babies can experience stress and hypoarousal. Toddlers and older children can have delayed milestones, inattention, impaired self-control, and affect disinhibition (National Institute on Drug Abuse, 2021).

**Alcohol**: Infants may be born with fetal alcohol syndrome, resulting in varying degrees of abnormal facies and intellectual disability.

**Opioids**: Newborns may experience neonatal opioid withdrawal syndrome (NOWS) which can consist of irritability, diarrhea, sweating, breathing difficulty, poor feeding, tremors, and seizures. Kids are also at an increased risk of inattention, lower IQ, and poorer academic performance (Conradt et al., 2019).

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# Synthetic Cathinones ("Bath Salts")

Synthetic cathinones are lab-made drugs designed to mimic traditional stimulant drugs of abuse such as cocaine and amphetamines. They are also falsely marketed and sold in place of MDMA. The drugs are chemically related to cathinone, which is a plant-derived monoamine alkaloid with effects similar to amphetamine. They are often significantly more potent than their non-synthetic counterparts and thus more dangerous. In order to avoid detection, the crystal or powder drugs are packaged and labeled as “bath salts,” “plant food,” or “jewelry cleaner” (National Institute on Drug Abuse, 2020).

# Synthetic Cannabinoids (“Spice”)

Starting around 2008, synthetic cannabinoids began to appear in herbal smoking mixtures sold online under names such as “Spice” and “K2.” These herbal preparations were marketed as a safe and legal alternative to marijuana. However, synthetic cannabinoids are significantly more dangerous than natural cannabinoids. They have a higher affinity for cannabinoid 1 and 2 receptors as compared to delta9-tetrahydrocannabinol (THC), making them more likely to induce a state of paranoid psychosis. Other possible effects include nausea, severe anxiety, panic attacks, tachycardia, and potentially fatal coronary ischemia (Fattore and Fratta, 2011).

# Drug-Induced Psychosis

Drug-induced psychosis can be caused by many different agents and typically resolves within a few weeks of the drug wearing off. However, among those who develop drug-induced psychosis, approximately 30% will develop a permanent psychotic illness.The drugs most associated with this phenomenon are hallucinogens, delta 9-THC, and amphetamines. One possible mechanism is thought to be related to the drugs inducing some of the same neurological changes seen in individuals prone to primary psychotic conditions. For example, the pathogenesis of schizophrenia has been found to involve synaptic and neuronal loss, and adolescent exposure to THC appears to produce similar changes in the developing brain (Osmio et al., 2019; Bara et al., 2021). Nevertheless, it remains unclear whether the drugs themselves are enough to produce the neurologic changes necessary for psychosis, or if the drug user must additionally have an underlying predisposition to psychosis.

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